REMARKS

Status of the Claims

Claims 33 and 53-82 are currently pending. Claim 1-32 and 34-52 have been canceled without prejudice or disclaimer of the subject matter claimed therein. Claims 33, 53-57, 61, 62, 64, 66, 68, 70-73, and 78 are withdrawn from consideration as being directed to a non-elected invention. Claims 58-60, 63, 65, 67, 69, 74-77, and 79-82 are under examination.

Rejection Under 102(b)

Claims 58, 60, 63, 65, 67, 69, 75, 77, and 79-81 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/04017 (Kresse, English Equivalent U.S. Patent 6,048,515).

Applicants respectfully point out that the claims are directed to methods of obtaining an active agent comprising specific method steps. To anticipate the claimed invention, the cited reference must disclose each of the recited steps. The method steps of Kresse does not include each of the steps recited in the claims. As an example, the Office Action acknowledges on page 5 of the Office Action that Kresse does not teach measuring the zeta potential or the isoelectric point of the composition. Accordingly, at a minimum, Kresse does not anticipate claims 75, 77, and 79-81 which include a step for measuring the zeta potential or the isoelectric point of the composition.

The Office Action alleges that Kresse discloses nanoparticles containing an iron-containing core, a primary coat of synthetic polymer, and a secondary coat of target polymer, and optional auxiliary pharmaceutical substances and/or adsorption mediators. The Office Action further points out the Kresse discloses that for the synthesis polymers, substances that contain negative charge carriers, such as a carboxy-derived dextran, in their molecule are preferred (see Office Action at page 4 and Kresse at column 12, lines 7-9).

Nevertheless, for Kresse to anticipate the claimed invention, Kresse must disclose each of the recited method steps. Kresse does not disclose the claimed invention because Kresse does not disclose the step of producing a composition with a zeta potential of about +30 mV to +65 mV at about pH 7.5, and Kresse does not disclose measuring the zeta potential of the composition.

The Office Action appears to infer that the nanoparticles of Kresse have a zeta potential that is equivalent to the zeta potential of the colloids obtained by the claimed methods. It is respectfully submitted that nanoparticles comprising an iron containing core, such as maghemite disclosed by Kresse, do not per se have a zeta potential as high as the claimed invention. Applicants submit with this response, the reference of Yu (Yu *et al.*, J. Materials Chem. 14: 2781-2786, 2004) which discloses in figure 3 that iron containing particles, such as maghemite, have a zeta potential of below +10 mV at a pH of 7.5. Moreover, as discussed above, Kresse discloses a preference for surrounding the iron containing core with a synthesis polymer that is negatively charged, which would lower the resulting zeta potential of the nanoparticle.

Likewise, the enclosed reference of Shaw (Shaw *et al.*, PNAS 105: 7387-92, 2008) discloses nanoparticles consisting of a supramagnetic iron oxide core and a covalently cross-linked dextran coating. Shaw, at Table S1 of the supporting information (also attached), discloses the zeta potential of these nanoparticles. None of the described nanoparticles, all of which contain a iron in the core, has a zeta potential of over +5 mV. Further, the nanoparticles of Shaw that contain a carboxy-derived dextran which are similar to those disclosed by Kresse as a preferred synthesis polymer, all have a negative zeta potential. Accordingly, one skilled in the art cannot find any equivalency or inherency with the feature of an iron core as disclosed by Kresse, with the claimed zeta potential of about +30 mV to +65 mV.

The Office Action further states that the compositions of Kresse are prepared by the same steps as the presently claimed invention. However, the nanoparticles of Kresse do not have the zeta potential recited in the claims. Thus, Kresse does not teach each of the steps recited in the claims.

Applicants respectfully point out that an example of using coated iron oxide particles as a cationic component is presented in Example 1.3 of the present specification. It is respectfully pointed out that iron oxide particles must be further treated or modified in order to have the zeta potential recited in the claims. In Example 1.3, iron oxide particles are coupled with a positively charged amino acid lysine to produce positively charged particles. The coupling of positively charged amino acid lysine with the iron oxide particles increases the zeta potential of the particles to within the range recited in the claims. Kresse does not disclose coupling the iron core to another positively molecule. Table 1 of the specification presents data evidencing that

HUVEC cell cultures (a model for angiogenic endothelial cells) have an increased uptake of the positively charged coated iron oxide particles in comparison to neutral and negatively charged iron oxide particles. Thus, the iron oxide particles can only be used as cationic components when they are modified to have a positive charge, for example as described in Example 1.3. of the specification.

Further, the method of Kresse is not directed to producing a composition that is effective for targeting an activated vascular site. The method of Kresse does not teach producing a composition that has an optimal zeta potential for specific targeting of an agent to an activated vascular site. Kresse does not disclose the optimal range of zeta potential that is effective for targeting an agent to an activated vascular site. Also, Kresse does not teach enhancing the efficacy of an active agent by associating an active agent with a cationic component to produce a composition having an optimal zeta potential for targeting an activated vascular site. Kresse also does not disclose producing compositions having an isoelectric point of above 7.5 for targeting activated vascular sites.

It is therefore respectfully submitted that the iron particles disclosed by Kresse do not inherently fall within the claimed zeta potential range. Further, Kresse does not disclose or suggest modifying their iron containing nanoparticles to have the zeta potential recited in the claims. Accordingly, Kresse does not anticipate the claimed invention. It is respectfully requested that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 59, 74, 76, and 82 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kresse, as applied to claims 58, 60, 63, 65, 67, 69, 75, 77, and 79-81, and in further view of Boehm (Boehm *et al.*, J. Pharm. Belg. 55: 40-48, 2000).

Claims 59, 74, 76, and 82, all depend directly or indirectly from claims 58 or 77. The deficiencies of Kresse are discussed above. The Office Action relies on Boehm to disclose the features of the dependent claims not disclosed in Kresse and to recite a method for determining the zeta potential of a composition.

Kresse, as discussed above, does not disclose a method for preparing a composition of cationic components with a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5. Kresse neither discloses determining the zeta potential of a

composition, nor discloses using cationic components that would fall within the claimed range of zeta potential. Further, the claimed zeta potential, as described in the specification, is useful for targeting the composition to activated vascular sites.

Boehm does not overcome the deficiencies of Kresse because Boehm does not disclose or suggest each of the features that are missing from Kresse. The reference of Boehm discloses the role of zeta potential in stabilizing dispersed systems. Boehm does not disclose the use of zeta potential to assist in targeting compositions to activated vascular sites. Boehm neither discloses a method of modifying an active agent to enhance its efficacy for targeting an activated vascular site nor teaches selecting a composition having a zeta potential in the range recited in the claims or having an isoelectric point above 7.5 for targeting an activated vascular site. Boehm does not disclose how to modify the iron particles of Kresse to achieve the claimed zeta potential range.

Further, the cited references do not provide a reason to combine their respective teachings of the references and to modify these teachings to obtain the claimed invention of associating an active agent with one or more cationic components to achieve the claimed zeta potential range for targeting an activated vascular site with a reasonable expectation of success. Accordingly, the cited references do not render the claimed invention obvious.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applieants respectfully request entry of the amendments, reeonsideration, and the timely allowance of the pending claims. A favorable aetion is awaited. Should thc Examiner find that an interview would be helpful to further prosecution of this application, she is invited to telephone thc undersigned at her convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Aecount No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

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